



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

By Certified Mail – Return Receipt Requested

CBER – 02— 002

Warning Letter

David L. Tousley, C.P.A.
Chief Operating Officer and Interim Chief Executive Officer
AVAX Technologies, Incorporated
4520 Main Street
Suite 930
Kansas City, Missouri 64111

Dear Mr. Tousley:

During the period of April 19, 2001, to May 25, 2001, Messrs. Mike M. Rashti and Robert B. Shibuya, investigators from the Food and Drug Administration (FDA) Philadelphia District Office, and Dr. Michele Keane-Moore, a microbiologist from FDA's Center for Biologics Evaluation and Research (CBER), conducted an inspection of AVAX Technologies' manufacturing facility located in Philadelphia, Pennsylvania. The purpose of the inspection was to review AVAX's activities as the sponsor and manufacturer of investigational autologous melanoma tumor vaccines. The inspection was conducted as part of FDA's Bioresearch Monitoring Program that includes inspections designed to review the conduct of research involving investigational products.

FDA reviewed your letter dated June 29, 2001, sent to the FDA Philadelphia District Office in response to the Form FDA 483 – "List of Inspectional Observations" issued to Gary D. Knappenberger, Director Global Regulatory Affairs, at the conclusion of the inspection. Our comments (in italics) are included below.

We determined that you have failed to fulfill the obligations as the sponsor of studies with investigational products, and violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published under Title 21, Code of Federal Regulations (CFR), Part 312. The applicable provisions of the CFR are cited for each violation.

You failed to fulfill the general responsibilities of sponsors. [21 CFR § 312.50].

- a. Your firm routinely manufactured tumor vaccines from tumor source materials that were previously shown to be non-sterile. You manufactured additional lots of vaccine from the original tumor source material even though the first lots of vaccine were proven to be contaminated. Your practice of releasing contaminated vaccines repeatedly exposed subjects to increased risk. The following examples are not a complete list.

On 6/1/00, a vaccine was manufactured and administered to subject 101-019-199-D-C. Results of sterility testing three days post manufacture found the original tumor source material to be contaminated with *Propionibacterium acnes*. Results were confirmed at 14 days post manufacture. Vaccines subsequently manufactured from the same tumor source material and administered on 6/9/00, 6/16/00, and 6/23/00 were also contaminated with *P. acnes*.

- ii. On 10/14/99, a vaccine was manufactured and administered to subject 101-001-196-WLR. Results of sterility testing three days post manufacture found the original tumor source material to be contaminated with *Enterococcus faecalis*. Results were confirmed at 14 days post manufacture. Vaccines subsequently manufactured from the same tumor source material and administered on 10/21/99, 10/28/99, and 11/4/99 were also contaminated with *E. faecalis*.
- iii. During the period of 3/14/00 to 1/4/01, there are at least four additional examples in which your firm manufactured subsequent lots of vaccine for the same subject even though a previous lot of vaccine was proven to be contaminated.

Your response letter dated June 29, 2001, states that the results of sterility testing are not known at the time the vaccine is manufactured and administered. The safety of parenteral drug products is contingent on their sterility and absence of pyrogenic substances.

While it may take up to 14 days to fully culture and identify a contaminated vaccine, preliminary results of contamination are available within 3 days. Yet, you continued to manufacture vaccines from contaminated starting materials. As a result, you permitted clinical investigators to administer contaminated vaccines to immunologically compromised subjects.

Further, we do not agree with your assertion that the immune response induced by BCG precludes the growth of contaminating bacteria.

Your response letter describes proposed corrections. Please provide specific details and supporting documentation as to how you will prevent manufacturing and administering contaminated vaccines to subjects in the future.

- b. You failed to inform clinical investigators that many vaccine preparations were contaminated with bacteria. As a result, the clinical investigators administered the contaminated vaccines to subjects. As a sponsor, you are responsible for ensuring that participating investigators are promptly informed of risks associated with the investigational vaccines.

Of the ~~—~~ culture-positive vaccines manufactured for ~~—~~ subjects under AVAX melanoma protocol #101, there are records that document only nine instances (for five subjects) when AVAX staff notified the clinical investigators that they had been shipped a contaminated vaccine.

Your response letter claims that all subjects who received a contaminated vaccine were closely monitored and that there were no reported adverse events. Records for the nine notifications document that clinical investigators received notification from one to eleven days after the contaminated vaccines were administered to the subjects. Please provide documentation of this special monitoring for each of the subjects.

- c. You failed to take appropriate corrective action to develop improved aseptic sampling procedures and to institute new training procedures to prevent the contamination of tumor source materials provided to AVAX. The AVAX investigation report entitled, "Evaluation of Sterility Tests as the In-Process Test for the Autologous Vaccine" dated 2/23/01, revealed that the tumor transport media had a microbial contamination rate of ~~—~~. AVAX concluded: "This result of high incidence of environmental contaminants indicates that the surgery and subsequent handling procedures of the tumor tissues are not performed under strict aseptic conditions. An improvement of these procedures is needed."

Your response letter indicates that you have or will take appropriate corrective action to this cited failure. Please provide a detailed description and timeline of the actions planned or implemented for improved aseptic sampling of tumor source materials, and provide documentation.

- d. Your firm consistently failed to comply with your written procedures for environmental monitoring (EM). Your firm consistently failed to investigate out-of-specification bio-burden data, and failed to perform ~~—~~ EM as required by SOP EMC-0001. Additionally, SOP EMC-0011, "Environmental Monitoring Report, and Investigation," requires an investigation and report for each alert/action level encountered during sampling.

During the period of 11/22/99 through 2/23/01, your firm produced at least ~~—~~ lots of non-sterile vaccine. The following table (not a complete list) documents that EM was not done on at least eight separate occasions during this period. Furthermore, no investigation was performed for any of the six instances in which the bio-burden exceeded specifications during this period.

TABLE: Deviations in Cleaning and Environmental Monitoring
on Days When Non-sterile Vaccine was Manufactured

<u>Date</u>	<u>Identified Microorganisms in Released Vaccine</u>	<u>Environmental Monitoring</u>	<u>Investigation Done</u>	<u>Equipment Cleaning</u>	<u>Production Room Cleaning</u>
11/22/99	<i>Propionibacterium acnes</i>	+ Bioburden*	No	Not done**	Not done**
11/29/99	<i>P. acnes</i>	Not done	No	Not done**	Not done**
12/13/99	<i>Coryneforme bacteria, P. acnes</i>	Not done	No	Not done**	Not done**
12/14/99	<i>Bacillus sp.</i>	+ Bioburden*	No	Not done**	Not done**
12/21/99	<i>Micrococcus sp., Enterococcus faecalis, Enterococcus raffinosus</i>	+ Bioburden*	No	Done	Not done**
1/11/00	<i>P. acnes</i>	+ Bioburden*	No	Done	Not done**
3/23/00	<i>P. acnes</i>	Not done	No	Not done**	Not done**
3/30/00	<i>Staph. warneri</i>	Not done	No	Not done**	Not done**
6/1/00	<i>P. acnes</i>	+ Bioburden*	No	Not done**	Not done**
6/16/00	<i>P. acnes</i>	Not done	No	Not done**	Not done**
6/23/00	<i>P. acnes</i>	+ Bioburden*	No	Not done**	Not done**
9/29/00	<i>Rhodotorula mucilaginosa</i>	Not done	No	Not done**	Done
12/21/00	<i>Staph. auricularis, Staph. capitis</i>	Not done	No	Not done**	Not done**
1/4/01	<i>Staph. hominis</i>	Not done	No	Done	Not done**
2/23/01	<i>P. acnes</i>	Testing incomplete	No	Not done**	Not done**
*Viable organisms exceeding action level (airborne, surface, or on gowning) in vaccine production areas					
**No documentation available to support if cleaning was done					

- e. Your firm consistently failed to comply with your SOP EMC-0017, "Cleaning of Manufacturing Booths and Equipment" and SOP EMC-0004, "Cleaning of AVAX Manufacturing Facility." The preceding table (not a complete list) illustrates instances for which your firm was unable to provide documentation of cleaning of the equipment or cleaning of the production rooms during the period of 11/22/99 through 2/23/01.

You state in your response that you implemented changes in personnel to correct the noted failures. Please provide a detailed explanation and supporting documentation of those additional corrective actions.

- f. Your firm failed to consistently produce vaccines that met the stated release specification of _____ For example, 56 of _____ entries in the "QA Release Deviation Report Log" document insufficient cell counts. In addition, AVAX's "Current Status/Treatment History" worksheets summarize the tumor and vaccine processing release-testing results for each subject. In examining the worksheets for four subjects, 25 of _____ vaccines had cell counts below _____. One vaccine had a cell count of _____ cells. You shipped these vaccines for administration to subjects even though the vaccines failed to meet the potency standard.

Furthermore, you failed to (1) investigate the cause of the low cell yield, (2) take appropriate and timely corrective action to prevent further occurrences of low cell yield, including enhancements to training of the clinical investigators, (3) notify clinical

investigators that they were receiving a vaccine that failed to meet the stated release specifications, and (4) communicate this information to FDA in your annual report. *We reject your explanation that this "process failure" is the "result of continued investigation and evolutionary development for the vaccine." Your response is inconsistent with your firm's internal SOPs. Your firm's deviation reports note that there were vaccine lots that did not meet the set release specification.*

We acknowledge that your firm has implemented changes in personnel. While these actions may address the release and reporting process deviations, they do not address the production failures. Please provide a detailed explanation and supporting documentation of additional corrective actions.

- g. On 11/30/99, during a telephone conversation with FDA about the manufacture of investigational autologous ovarian tumor vaccines, your firm committed to perform a _____ on the final tumor vaccine before it was shipped to the clinical investigators. Your firm promised to release and ship only those vaccines that showed no bacteria in a _____ prior to administration to subjects.

Eleven months later, on 11/8/00, your firm validated the procedure AV-0001R _____ Method for the Detection of Gross Microbial Contamination of Autologous Vaccine Products." Even after the procedure was approved, your firm either continued to release vaccine lots without considering the results from the validated _____ procedure, or did not perform the _____ procedure on all lots.

Not only did your firm delay in developing a _____ procedure, once developed, your firm failed to consistently implement the procedure to test the vaccines before you shipped them to the clinical investigators. This practice placed subjects at risk of illness or injury from contaminated vaccines.

Your written response contends that the requirement for _____ release testing was only for investigational ovarian tumor vaccines. However, you make no specific distinction between ovarian and melanoma vaccines in your standard operating procedure (SOP) which states: "The _____ method is to be used as the release test of the autologous vaccines produced by AVAX Technologies to assess the sterility of the product."

Please explain why your firm failed to perform the _____ test for investigational vaccines produced after November 8, 2000, regardless of the type of tumor source material. Please provide a detailed explanation and supporting documentation.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the law and applicable regulations. You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in enforcement action without further notice. These actions could include termination of Investigational New Drug Applications, and/or injunction.

You should notify this office in writing within fifteen (15) business days of receipt of this letter of the specific actions you have taken to correct the noted violations. If corrective action cannot be completed within fifteen (15) business days, state the reason for the delay and the time within which corrections will be completed. Your response should include any documentation necessary to show that correction has been achieved. Your response to this letter should be separate from your response to the FDA letters dated April 12, 2001, and April 13, 2001. Your response should be sent to the following address:

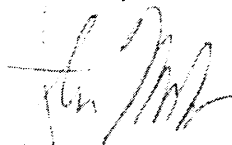
Robert L. Wesley (HFM-664)
Division of Inspections and Surveillance
Food and Drug Administration
1401 Rockville Pike
Rockville, Maryland 20852-1448
Telephone: (301) 827-6221

We request that you send a copy of your response to the following FDA District Offices:

Thomas D. Gardine, Director
Food and Drug Administration
900 US Customhouse
2nd & Chestnut Streets
Philadelphia, Pennsylvania 19106

Charles W. Sedgwick, Director
Food and Drug Administration
11630 West 80th Street
Lenexa, Kansas 66217-3338

Sincerely,



Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Cc: Charles W. Sedgwick, Director
Thomas D. Gardine, Director